

# Exploring the Differences in the Genetic Underpinnings and Inheritance Patterns in JME and FAME for Improvement in Diagnostic Accuracy and Correct Treatment

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Juvenile Myoclonic Epilepsy (JME) and Familial Adult Myoclonus Epilepsy (FAME) are both considered genetically based myoclonic epilepsies; they both feature similar symptoms, with the primary difference being age of onset. Difficulty distinguishing between these two disorders leads to misdiagnoses. Using a literature review approach, this paper explores each epilepsy's respective genetic factors, inheritance patterns, and, if applicable, epigenetic mechanisms to better understand why JME and FAME present at different ages despite symptom similarity to improve diagnosis and treatment for both. Information was sourced from Google Scholar between 2017 and 2025 about JME, FAME, epigenetics, and factors in the age of onset. As a result of these methods, the following was found: JME can be traced back to the Mendelian-illustrative genes GABRA1 and EFHC1, which both disrupt neuronal transmission, neuron migration, microtubule stability, and apoptosis. Since JME is a heterogeneous condition, the distribution and variability among different family trees cause speculation as to whether JME is considered an autosomal dominant disease or one with a more complex inheritance pattern. Alternatively, FAME is caused by intronic repeat expansions in four genes: SAMD12, STARD7, MARCH6, and YEATS2, each of which is linked to a different subtype. Although not yet proven, DNA methylation and histone modifications may be epigenetic mechanisms of FAME, as they are found in other neurological repeat expansion disorders, along with RNA toxicity and modified chromatin structures. FAME is considered heterogeneous and an autosomal dominant disorder. Understanding these genetic differences lays the foundation for the development of better diagnostic tests/practices and targeted therapeutics for each disorder.

**Keywords:** Juvenile Myoclonic Epilepsy, Familial Adult Myoclonus Epilepsy, Epigenetics, Genes, Age of Onset, Inheritance Pattern

## Introduction

Epilepsy is a neurological disorder where an individual experiences occasional seizures due to sudden spikes in electrical activity in the brain. Seizures are involuntary movements where the individual may undergo intense bodily shaking, myoclonic jerks, stiffening, and/or a loss of consciousness. Epilepsy is divided into three types: focal, unknown, and generalized epilepsy.

Generalized epilepsy is classified by seizures that occur in the entire brain rather than one specific area. This type of epilepsy features motor, sensory, autonomic, and cognitive symptoms. It always results in loss or impairment of consciousness and occurs within both hemispheres of the brain, thus affecting the body bilaterally, unlike focal epilepsy, which tends to affect one hemisphere and presents unilaterally regarding bodily dysfunction<sup>1</sup>. A subcategory of generalized epilepsy, Idiopathic Generalized Epilepsy (IGE), accounts for

types of epilepsies that are thought to be caused by genetics and do not feature any structural brain abnormalities that can be detected via brain imaging<sup>2</sup>. The four main types of IGE are Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Idiopathic Generalized Epilepsy with Tonic-Clonic Seizures Alone (GTCS alone), and Juvenile Myoclonic Epilepsy (JME). The first two types, CAE and JAE, similarly consist of absence seizures, in which the person will experience brief conscious moments during a seizure, as well as many staring spells throughout the day. GTCS alone causes the person to undergo a loss of consciousness, stiffening of the body, and jerks, and normally starts before the age of 25<sup>2</sup>. JME is considered a lifelong disorder, beginning between the ages of 12-18, and is commonly triggered through sleep deprivation or awakening. The primary symptoms are myoclonic seizures, accompanied by tonic-clonic seizures and absence seizures at times<sup>3</sup>. JME is also "diagnosed in around 5-10% of all cases of epilepsy and 18% of all cases with [GGEs]," impacting around 0.1% of people around the world<sup>3,4</sup>. Addi-

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tionally, JME has not exhibited any lethal traits on patients, leading to lesser amounts of studies conducted on its mortality rates<sup>5</sup>. Familial Adult Myoclonus Epilepsy (FAME), while not considered to be a direct IGE, is both genetically based and is considered a type of generalized epilepsy<sup>6</sup>. It is a rare autosomal dominant neurological disorder, usually beginning in adulthood and triggered by flashy visuals, emotional stress, or sleep deprivation. Due to often being overlooked, studies regarding FAME's epidemiology show it impacts less than 1 in 35,000 individuals<sup>7</sup>. However, the severity of symptoms tends to increase with age, including the slow progression of tremor, myoclonus, and various other disabilities, though with anti-seizure medication, most patients have normal life expectancies<sup>8</sup>. Due to the various components of each of these types of genetic and generalized epilepsies, this paper will explore the differences in genetic contribution and inheritance patterns between JME and FAME to uncover what factors enable such a similar clinical presentation with differing ages of onset between the disorders.

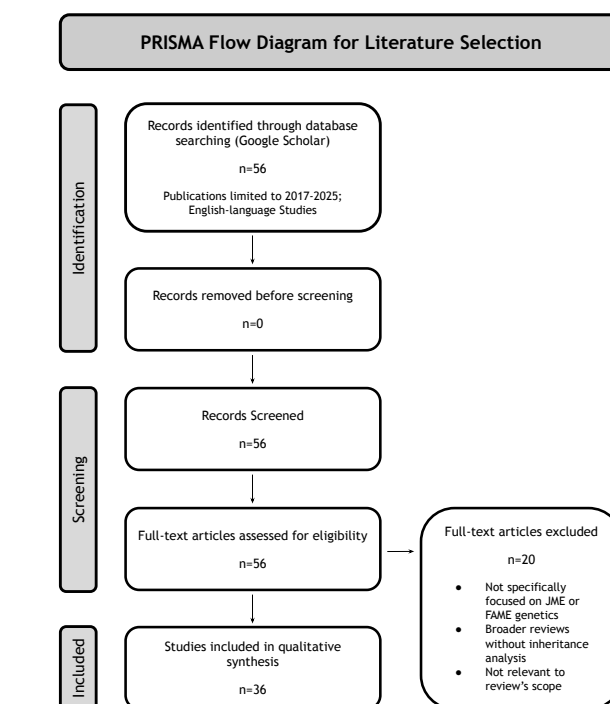
## Methods

The method used to approach this research question is a literature review, where an analysis of various research papers related to JME and FAME and the comparison of each of their genetic linkages was conducted. Using key terms such as "Juvenile Myoclonic Epilepsy," "Familial Adult Myoclonus Epilepsy," and "age of onset," the Google Scholar database was used to find research papers published between 2017 and 2025 in order to capture the most recent understandings related to epilepsy. Papers with the most citations, relevance, and information were selected specifically for this study. Additionally, references from specific parts of these papers were used to find even more information, such as finding a more detailed paper on epigenetics in epilepsy. As for the main papers, there was at least one paper discussing each of the types of epilepsy in detail, alongside one paper detailing the genetics involved with epilepsy, allowing efficient identification of how that information is presented in the previous articles. Furthermore, recognition and criticism of any potential gaps in information in the research papers were covered in this paper.

## Results

### Juvenile Myoclonic Epilepsy

JME, alongside myoclonic jerks (MJs) and seizures, is classified by widespread, high-amplitude EEG polyspike waves that occur in both hemispheres of the brain<sup>9</sup>. According to this study, these MJs frequently happen after sleep when one has complete consciousness, and they predominantly take place in



**Figure. 1** A structured search of the Google Scholar database (2017-2025; English-language studies) identified 55 studies. After a full-text review, 20 articles were excluded for lack of focus on JME and FAME genetics or lack of inheritance analysis. Thirty-five studies were included in the final qualitative synthesis.

the upper body, especially the dominant hand. 80-95% of people undergo the tonic phase of tonic-clonic seizures, meaning the stiffening of muscles and loss of consciousness, after experiencing numerous MJs in higher amplitudes and frequencies<sup>10</sup>. Patients may also experience absence seizures with impaired consciousness, based on 10-40% of JME cases in the study<sup>9</sup>.

In addition to sleep deprivation and awakening, JME is often caused by alcohol and drug consumption and stress. It may also be caused by the menstrual cycle, visual and photic stimuli, or coordinated motor activities. Furthermore, while antiepileptic drug treatment (AED) is normally effective, a third of patients respond negatively, and many who attempt to stop AED treatment regain past symptoms and have frequent seizures again<sup>9</sup>. This recurrence demonstrates the need to better understand the contributing factors of JME and FAME so that more effective interventions can be developed. The following sections will highlight the genes and their developed mutations and/or variants that have caused or triggered JME and its inheritance pattern(s).

**Table 1** This table summarizes the age-of-onset in JME Patients across multiple demographics, such as sex and age, from primary cohort data. Adapted from<sup>11</sup>.

| Characteristics samples | Average age, M±m               | Me (Q25:Q75)      | Average age of onset of JME, M±m | Median age of onset of JME, Me (Q25:Q75) |
|-------------------------|--------------------------------|-------------------|----------------------------------|------------------------------------------|
| Total                   | 27,74 ± 0,62                   | 27,0 (22,0: 33,0) | 13,52 ± 0,38                     | 14,0 (11,0: 16,0)                        |
| Male, n = 52            | 26,3 ± 1,14; <i>p</i> = 0,131  | 24,0 (20,0: 32,3) | 14,16 ± 0,53; <i>p</i> = 0,205   | 14,0 (12,0: 16,0)                        |
| Female, n = 125         | 28,36 ± 0,74; <i>p</i> = 0,131 | 28,0 (22,0: 33,0) | 13,25 ± 0,48; <i>p</i> = 0,205   | 13,0 (10,0: 16,0)                        |

FAME

FAME, similar to JME, is a type of generalized epilepsy and is rooted in genetics, but it is not considered a type of IGE. However, it is considered a Genetic Generalized Epilepsy (GGE), which is a broader category for generalized epilepsies with genetic causes, even encompassing the IGE category. It is a rare autosomal dominant condition, meaning that it can run through generations, impacts both males and females, and children of affected parents have a 50% chance of receiving it<sup>6</sup>. FAME has been associated with four loci on chromosomes 2, 3, 5, and 8 and is characterized by giving individuals between 10 and 60 tonic-clonic seizures and cortical tremor. The cause specifically stems from pentanucleotide repeat expansions in intronic TTTC and TTTA in a noncoding region, meaning that these DNA sequences repeat too many times in an area of the gene that does not build protein, messing up how the gene is used and leading to FAME<sup>6</sup>. Reported family-level data further demonstrate the broad and variable age-of-onset range seen in FAME, as shown in Table 2.

Similar to JME, FAME is also triggered by alcohol consumption, photic stimuli, and emotional stress<sup>6</sup>. Some symptoms that may accompany it include photosensitivity, depression, and migraines. Additionally, cortical tremor and myoclonic jerks worsen over time, and individuals may face frequent cases of status epilepticus as well.

Genetic Contributions

JME

Two genes closely associated with the development of JME are GABRA1 and EFHC1. Due to their broader polygenic and heterogeneous landscape, their nature will allow for the better prediction of patterns, data collection, and the identification of mutations given past studies. This paper will go into depth about the gene itself and how its variants have been shown to impact JME.

GABRA1: Variants and Effects

The gamma-aminobutyric acid A receptor alpha 1 (GABRA1) gene helps make a part of the GABAA receptor protein, the alpha-1 (α1) subunit, by providing instructions for its formation, therefore allowing the protein to slow down brain cells'

activity<sup>13</sup>. Specifically, the neurotransmitter it responds to, gamma-aminobutyric acid (GABA), is the primary inhibitory neurotransmitter. As GABA and GABAA bind together, an ion channel opens, chloride ions flow in and enter the neuron, slowing activity in the brain. GABA signaling tends to reduce the number of seizures the individual may experience and aids in maintaining usual brain rhythms. GABAA is made up of five different subunits, and the combinations between them can determine how the receptor functions in different parts of the brain<sup>13</sup>.

Variants and mutations of the GABRA1 gene can impact how the calming signals work, with some resulting in epilepsy, especially childhood forms of epilepsy. While the eight variants assumed to be closely linked to epilepsy are L49H, P59L, W97R, D99G, G152S, V270G, T294R, and P305 in Arslan's (2023) paper, Gilsoul et al.'s (2019) paper suggests that the specific mutation for JME is A322D, and according to Ma et al.'s (2006) study, no mutations were found in GABRA1 in relation to JME.

The mutation A322D, which indicates alanine is substituted for aspartic acid at position 322, is only found in people with epilepsy<sup>14</sup>. Based on a study conducted on a family of French-Canadian descent, it was the first mutation to be found in JME following an autosomal dominant inheritance pattern. Furthermore, when the researchers expressed the A322D mutant GABRA1-containing GABAA receptor in heterologous cells and found that it caused the receptor to become defective at folding and trafficking, lowering cell-surface expression and failing to calm neural activity.

In contrast, another paper conducted a broader study on 54 families of European/Caucasian descent with fewer patients per family, finding no specific mutations in relation to GABRA1 related to JME. Instead, they found common, harmless genetic variants in GABRA1, leading them to conclude that many genes may be involved with JME<sup>15</sup>.

EFHC1: Variants and Effects

The EF-hand domain-containing protein 1 (EFHC1) gene provides instructions to make the protein EFHC1, which interacts with another protein that serves as a calcium channel, enabling calcium cations to cross the cell membrane<sup>16</sup>. The cations' movement is essential for neuronal signaling in the brain and in other areas of the nervous system. The EFHC1 gene is

**Table 2** This table summarizes family-level age-of-onset data and associated seizure features in familial adult myoclonus epilepsy (FAME). The broad range of onset ages illustrates the greater heterogeneity and typically later presentation of FAME compared with JME. Adapted from<sup>12</sup>.

| Family | Nationality                                 | Total affected  | Mean onset (range)          | Myoclonus/CT            | TCS           | Focal Sz    | References |
|--------|---------------------------------------------|-----------------|-----------------------------|-------------------------|---------------|-------------|------------|
| 1      | Australian/New Zealand of European Ancestry | 55              | 18.6 y [4–59,60 y]          | 55/55 (100%)            | 8/55 (15%)    | 2/55 (4%)   | 2          |
| 2      | Italian                                     | 2               | 15–25 y                     | 2/2 (100%)              | 2/2 (100%)    | 0/2 (0%)    |            |
| 3      | Italian                                     | 4               | 2–18 y                      | 4/4 (100%)              | 4/4 (100%)    | 2/4 (50%)   | 12         |
| 4      | Italian                                     | 11              | 22.3 y [12–49,50 y]         | 11/11 (100%)            | 11/11 (100%)  | 3/11 (27%)  | 4,17       |
| 5      | Italian                                     | 25              | 26.6 y [5–39,40 y]          | 25/25 (100%)            | 10/25 (40%)   | 0/25 (0%)   | 38         |
| 6      | Italian                                     | 12 (3 studied)  | 12 y [8–17,18 y]            | 11/12 (91.6%)           | 6/12 (50%)    | 1/12 (8.3%) | 9,39       |
| 7      | Italian                                     | 4               | 22.75 y [10–35,36 y]        | 4/4 (100%)              | 3/4 (75%)     | 0/4 (0%)    |            |
| 8      | Italian                                     | 10 (6 studied)  | 18.5 y [17–19,20 y]         | 6/6 (100%)              | 4/6 (66.6%)   | 0/6 (0%)    | 40         |
| 9      | Italian                                     | 13 (11 studied) | 17 y [12–21,22 y]           | 11/11 (100%)            | 9/11 (81.1%)  | 0/14 (0%)   | 41         |
| 10     | Italian                                     | 16 (14 studied) | 15.8 y [13–19,20 y]         | 14/14 (100%)            | 10/14 (71%)   | 0/14 (0%)   | 41         |
| 11     | Italian                                     | 10 (5 studied)  | 15.5 y [13–17,18 y]         | 5/5 (100%)              | 4/5 (80%)     | 0/5 (0%)    | 42         |
| 12     | Italian                                     | 21 (17 studied) | 39.2 y [24–55,56 y]         | 17/17 (100%)            | 13/17 (76.4%) | 0/17 (0%)   | 43         |
| 13     | Italian                                     | 3               | 17.7 y [12–22,23 y]         | 3/3 (100%)              | 1/3 (33%)     | 0/3 (0%)    | 42,44      |
| 14     | Italian                                     | 3               | 16.3 y [15–18 y]            | 3/3 (100%)              | 3/3 (100%)    | 0/3 (0%)    | 44,45      |
| 15     | Italian                                     | 4               | 30.3 y [18–48,49 y]         | 4/4 (100%)              | 3/4 (75%)     | 2/4 (50%)   | 17         |
| 16     | Iraqi of Sephardic Jewish ancestry          | 15 (10 studied) | 21 y [12–31,32 y]           | 10/10 (100%)            | 4/10 (40%)    | 2/10 (20%)  |            |
| 17     | Israeli of Sephardic Jewish ancestry        | 2               | 21 y [21 y]                 | 2/2 (100%)              | 2/2 (100%)    | 0/2 (0%)    |            |
| 18     | South African of European ancestry          | 24 (15 studied) | 15.8 y [11–19,20 y]         | 15/15 (100%)            | 7/15 (47%)    | 1/15 (7%)   | 46         |
| 19     | French/Spanish                              | 13              | 41 y [30–59,60 y]           | 13/13 (100%)            | 8/13 (62%)    | 0/13 (0%)   | 13,47      |
| 20     | French                                      | 7 (2 studied)   | 20 y (n=1); Childhood (n=1) | 2/2 (100%)              | 1/2 (100%)    | 0/2 (0%)    | 9          |
| 21     | Syrian                                      | 1               | 20 y                        | 1/1 (100%)              | 1/1 (100%)    | 0/1 (0%)    |            |
| 22     | Italian                                     | 11 (10 studied) | 25.1 y [14–39,40 y]         | 9/10 (90%) <sup>a</sup> | 4/10 (40%)    | 1/10 (10%)  |            |

thought to aid in calcium homeostasis and may even cause apoptosis.

Many variants and/or mutations in EFHC1 have been found in relation to JME. The aforementioned study suggests that the EFHC1 variant R221H may have uncertain significance regarding JME and epilepsy in general<sup>15</sup>. A different study shows that three EFHC1 variants, R182H, D210N, and F229L, may cause JME<sup>17</sup>.

The first paper explains that an R221H mutation means the amino acid arginine at position 221 is instead substituted for histidine. Position 221 is close to the EF-hand domain, and therefore, the calcium-binding process. However, the study also found that the mutation was found in one of the JME patients and the patient's unaffected parent, causing uncertainty regarding its influence on JME<sup>15</sup>. This caused researchers to conclude that it has uncertain significance or may work with other genetic or epigenetic factors.

The same mutation, replacing arginine with histidine, can occur at residue 182. According to Raju et al. (2017), R182H disrupts microtubule binding by weakening EFHC1's ability to attach to microtubules, which helps with neuron shaping

and division. During metaphase in mitosis, the mutation also causes misaligned spindles and chromosomes, leading to deformed brain cell development. Additionally, in cells similar to neurons, R182H shortens neurites, the branches that neurons use to signal and communicate, also damaging brain circuit formation<sup>17</sup>. Another source also mentions how the swapping of arginine and histidine can impair EFHC1's protein shape, lead to unstable amounts of apoptosis, and, as a result, interfere with brain structure. It can also excite the brain by causing extra spikes in electrical activity, causing seizures, especially in people with JME. In the variant D210N, 210 is the position of the amino acid in the protein, and "N" stands for the new amino acid that replaces D, which is asparagine<sup>17</sup>. D210N impacts the same processes as R182H, except it affects cell shape more prominently and shortens neurites, while R182H messes with microtubules' binding efficiency. Unlike D210N and R182H, F229L, in which "F" stands for the original amino acid, phenylalanine, and "L" stands for the replacement, leucine, is located outside the EF-hand domain and is less severe. Even with its location, it is still in an essential region of EFHC1, still disrupting metaphase and the spindles,

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reducing neurite length, and influencing cell deformities<sup>17</sup>.

## **FAME**

Four major genes known to play a role in the development of FAME are SAMD12, STARD7, MARCH6, and YEATS2. This study will explore the gene itself in depth and how its intronic repeat expansions cause FAME.

### ***SAMD12: Mutations and Effect***

Sterile Alpha Motif Domain Containing 12 (SAMD12) gene encodes a protein that is around 201 amino acids long that contains a sterile alpha motif (SAM) domain and is located on chromosome 8<sup>18</sup>. The SAM domain spans around 70 amino acids since it helps regulate proteins in RNA interactions<sup>19</sup>. While lacking in proper experiments and direct research, SAMD12 is predicted to partake in the cell surface receptor protein tyrosine kinase signaling pathway, which helps in cell communication systems used by cells with proteins on their surfaces that provide instructions on growth, repair, and reactions to the environment<sup>20</sup>. Additionally, it may be active on the cytoplasmic side of the plasma membrane, meaning that its presence may interfere with brain and cell signaling, and possibly lead to seizures. Furthermore, some suggested molecular and biological functions it may perform are protein binding, sequence-specific DNA binding, and the transcription, proliferation, and stimulus response of cells<sup>20</sup>. All of SAMD12's mutations, especially the intronic repeat expansions, point to its involvement with FAME1, a subtype of FAME.

According to another study, FAME1 is directly caused by the non-protein-coding mutations in intron 4 of SAMD12<sup>21</sup>. The repeat sequence encompasses a repeating stretch of the pentanucleotide TTTTA, in which the “T” stands for thymine and the “A” stands for adenine. The harmful inserted TTTCA repeat, in which the “C” stands for cytosine, is inserted inside and/or beside the TTTTA repeat expansion, causing the mutation. Since the mutation occurs in a region that does not impact the protein, SAMD12's function is not the cause of FAME1, but is instead determined by the repeat sequence, meaning that FAME1 is pathogenic<sup>22</sup>. This indicates that the longer the repeats of the mutation, the earlier the onset and the more severe the symptoms of FAME1 in an individual, especially when TTTCA is between two TTTTA repeat sequences. As the repeat expansions accumulate, they can cause RNA toxicity, which can disrupt gene regulation and expression over time. The continuous disruption possibly explains why longer repeat expansions are linked to the specific onset and exacerbated symptoms of FAME and its types, such as MARCH6 and its relation to FAME3.

### ***STARD7: Mutations and Effect***

The StAR-related lipid transfer domain protein 7 (STARD7) gene is located on chromosome 2, and protein 7 has a StAR-related lipid transfer (START) domain, which helps the protein move lipids to and from cells and within cells, such as to the mitochondria<sup>23</sup>. As a lipid transporter, STARD7 especially helps in moving phosphatidylcholine, a type of phospholipid. In addition, the gene influences cell growth and development, specifically helping in cell proliferation, transportation, and differentiation<sup>24</sup>. Additionally, STARD7's gene expression is regulated by pathways such as Wnt/ $\beta$ -catenin and steroidogenic factor-1 (SF-1)<sup>23</sup>.

According to Corbett et al. (2019), a repeat expansion in a non-coding region of the gene was the mutation in the gene STARD7 that caused FAME2. Similar to SAMD12, the repeat expansion that caused the mutation was a pentanucleotide, ATTTC, which was inserted into the TAAAA sequence. However, individuals with FAME2 experience a longer repeat expansion of TAAAA than normal people and the insertion of the new, harmful ATTTC sequence<sup>12</sup>. Due to its existence in a non-protein-coding region, the mutation does not impact STARD7's gene expression. However, by being transcribed into abnormal RNA, it can cause the RNA to form toxic structures that trap RNA-binding proteins and disrupt gene regulation, which can eventually lead to seizures and jerks.

### ***MARCH6: Mutations and Effect***

The gene Membrane-Associated Ring-CH-Type 6 (MARCH6), is located on chromosome 5 and is responsible for creating a protein that helps break down other proteins in the endoplasmic reticulum (ER). This process is conducted using the molecule ubiquitin, since it belongs to the E3 ubiquitin ligase family<sup>25</sup>. Specifically, it helps in moderating cholesterol and lipid metabolism by breaking down proteins such as squalene epoxidase (SQLE), as well as disposing of unnecessary proteins in cells. RNA toxicity then causes MARCH6 to become unstable in the genome, especially in nerve cells, leading to symptoms of FAME3. Exactly like SAMD12 and STARD7, the long repeat expansions, TTTCA and TTTTA, build up in the non-coding regions, or introns, of the gene, causing RNA toxicity. It disrupts the gene's regulation, causing MARCH6 to become unstable in the genome, especially in nerve cells, leading to symptoms of FAME3.

### ***YEATS2: Mutations and Effect***

YEATS Domain-Containing 2 (YEATS2) is a gene located on chromosome 3 that encodes a protein that is part of the ATAC histone acetyltransferase complex, aiding in controlling how DNA is packaged and used in cells<sup>26</sup>. In simpler terms, YEATS2 turns genes on and off by helping alter chromatin, which is DNA wrapped around protein. Like the other genes

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in relation to FAME, long repeat expansions of TTTTA and insertions of TTTCA in the first intron of the gene were found in those with FAME4. The fall of YEATS2 in neurons caused failed responses to stress, movement issues, changes in social behavior, and seizure-like actions<sup>27</sup>. These symptoms were most likely caused by reduced dopamine production, leading researchers to believe that L-DOPA, a dopamine-producing compound, could help. This suggests that the gene's loss of function in neurons may contribute to symptoms seen in FAME4.

## **Inheritance Patterns of JME and FAME**

### ***JME: Inheritance Patterns***

According to Delgado-Escueta et al. (2012), JME has a Mendelian inheritance pattern, meaning that JME can be passed down from parent to offspring in one of two predictable patterns, autosomal dominant (AD) and autosomal recessive (AR). AD traits are easier to inherit, as the individual only requires one copy of the gene to express the trait and it is passed consistently from parent to child. AR traits are harder to get, requiring two copies of the gene for expression, and they may skip generations. In Delgado-Escueta et al.'s (2012) study, 49% of JME families were shown to have vertically inherited clinical and EEG traits continuously over generations, indicating an AD pattern. Some genes found to be associated with Mendelian JME were GABRA1, EFHC1, BRD2, etc. However, the other 51% of families demonstrated more complex hereditary patterns, in which one single gene by itself may not influence an individual's likelihood to express JME. Instead, they may require several variants and/or mutations to develop the disorder<sup>28</sup>.

Revisiting GABRA1, Cossette et al.'s (2002) paper found that every person from the French-Canadian family studied expressed JME in all four generations. Furthermore, it was stated that those affected were heterozygous, meaning that they had one normal copy and one mutated copy of GABRA1, implying that JME may be an AD disorder. Additionally, Suzuki et al. (2004) suggests the AD pattern in terms of the gene EFHC1, finding mutations in this gene among the affected family members. These mutations were also found in unrelated families, but most significantly showed high penetrance in those with the gene, meaning that most affected people will develop JME.

In contrast to the indication of JME being an AD disorder, Gilsoul et al. (2019) and Yacoub et al. (2025) argue that JME is instead not strictly Mendelian but may also follow a more complex inheritance pattern, similar to Delgado-Escueta et al.'s (2012) paper. They point out how the disorder does not always pass down consistently as an AD inheritance pattern should, highlighting how some JME parents don't even have a family history, and that even within JME families, the

genetic variant is not always shared. Additionally, Gilsoul et al.'s (2019) paper emphasizes that most of the time, JME is heterogeneous, being caused by many different genes, but it may also be caused by only one specific gene, such as EFHC1. This rarity is more frequently seen in familial JME, in which the AD pattern is also more predominantly present. On the other hand, most JME cases are stated to be sporadic and heterogeneous without a clear inheritance pattern<sup>29</sup>. While family inheritance patterns do show clustering of risk, they do not clearly predict the age of symptoms' onset in families, as JME is heterogeneous and has incomplete penetrance.

Incomplete penetrance is when individuals who possess a disease-causing gene develop the disease while others do not<sup>30</sup>. As many studies, especially Delgado-Escueta et al. (2012), discuss, some people who carry the EFHC1 gene, for example, may not experience clinical seizures but will display abnormal EEGs. Such people are referred to as "non-penetrant individuals," meaning that they carry the risk but do not express the disorder, even within a family demonstrating an AD JME inheritance pattern, which is called "variable expressivity". Additionally, this implies that many different environmental and genetic factors influence whether someone with a genetic mutation linked to epilepsy actually inherits the disease, and that mutation in genes such as EFHC1 is necessary for JME development but not always sufficient.

### ***FAME: Epigenetic Mechanisms***

DNA methylation is when a methyl group is added to DNA, specifically at a cytosine nucleotide, which is done by enzymes called DNA methyltransferases (DNMTs), and turns genes on and off<sup>31</sup>. The DNMTs DNMT3a and DNMT3b place the new methyl "tags", and DNMT1 keeps track of those tags during cell division, which results in genes usually turning off, especially in gene promoter areas, but sometimes, it may activate genes as well. In epilepsy, too much methylation, or rather hypermethylation, can silence important genes and cause seizures, while impairing methylation can reduce seizures.

Of the four types of histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, acetylation and methylation have been unusually found in the hippocampus and temporal lobe regions of the brain in relation to epilepsy<sup>31</sup>. Acetylation opens DNA and activates gene regulation, while methylation can lock, suppress, and/or activate gene regulation. An AED, called Valproic acid (VPA), blocks the enzymes that block acetyl groups and therefore prevents seizures<sup>31</sup>. In terms of methylation, the enzyme EZH2 adds methyl tags to histones, making chromatin structures tighter; this leads to the shutting off of genes such as glutamate receptors, also causing seizures. However, given unclear relations to FAME, such processes are currently only suspected to play a role in FAME.

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As stated before, FAME is caused by RNA toxicity and changes in chromatin structure, as these processes interfere with important sequences or shut down important genes that may contribute to the age of onset<sup>31</sup>. A neurodegenerative disorder, Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), which mostly targets older adult men, can cause tremors, and coordination and memory issues, and is caused by CGG repeat expansions in the gene FMR1. The expansion can range from 55 to 200 repeats<sup>32</sup>. Additionally, a neurological disorder, myotonic dystrophy 1 (DM1), impacts skeletal and smooth muscle, especially those of the eyes, heart, endocrine system, and nervous system<sup>33</sup>. It demonstrates CTG trinucleotide repeat expansions in its DMPK gene, which then condenses chromatin around the area through DNA or histone methylation<sup>34</sup>. The main pathogenic repeat in this disorder is CTG, as CGG serves more as a variant interruption rather than a primary source; however, they may have similar effects on the phenotype as they are both part of the same repeat tract structure. While such factors have not been found specifically in FAME, such epigenetic factors have been shown to play a role in other repeat expansion disorders and may pose a strong possibility for FAME in the future. Furthermore, these mechanisms are known to cause tremors and impact the nervous system, similar to FAME.

### ***FAME: Inheritance Pattern***

FAME is an AD disorder, meaning that an individual only requires one copy of the gene to express the disorder, and it consistently runs through generations of families<sup>6</sup>. This is backed by Corbett et al.'s (2023) study, stating that all the people with the repeat expansion in the gene STARD7 showed symptoms of FAME. However, variable expressivity is also present in FAME, as discussed in Scheffer's (2019) paper and Corbett et al.'s (2023) paper. Even though myoclonus and tremor are present in all types of FAME, their severity is highly variable, even within the same family. In the first study, families are said to have different amounts of people with GTCS, from around 15%-100%<sup>35</sup>. Additionally, symptoms such as tremor become more severe with age, and in certain families, focal temporal lobe seizures occur, which are not seen in many others. In Corbett et al.'s (2023) study, anticipation in FAME was also discovered, meaning that the disease was more severe for younger generations in a family.

In addition to being an AD disorder, FAME is also considered a heterogeneous one, meaning that it is caused by different mutations in different genes. This can be seen through the studies above about the four genes, SAMD12, STARD7, MARCH6, and YEATS2, which are mutations on different chromosomes. Each gene and its respective mutation caused a different subtype of FAME as well. This implies that more than one gene must be tested in order to diagnose FAME and that the location and structure of the repeat matter more than

the mutated gene itself. FAME's AD inheritance pattern suggests strong family clustering, though similar to JME studies, there is a significant lack of literature to show how inheritance patterns shape ages of onset.

### **Factors Leading to Differing Ages of Onset**

JME, as stated above, is typically reported to start between ages 12 and 18, while FAME can start anywhere between ages 10 and 60, an evidently broader range than JME. This overlap within the age range is most likely the cause of confusion and misdiagnoses between the two epilepsy types. JME is a result of genetic mutations that influence neuron transmission, neuron migration, microtubule stability, and apoptosis, which all impact developing parts of the brain such as the thalamocortical and frontal lobe networks, especially during puberty when hormonal and neuronal excitability is at its highest<sup>28</sup>. On the other hand, FAME is a result of intron repeat expansions, where the longer the repeat expansion, the earlier the symptoms start to show<sup>12</sup>. Epigenetics can also influence when FAME begins, while JME is more spontaneous<sup>28</sup>.

### **Discussion**

This literature review was conducted in order to illustrate the differences that lie between two genetic, generalized epilepsies, JME and FAME, and their similarities in terms of genetic contribution and inheritance patterns.

Given their status as generalized epilepsies, both JME and FAME occur in both hemispheres of the brain, and being genetic epilepsies, the two have demonstrated strong genetic components as well. Additionally, JME and FAME awaken during adolescence to early adulthood, and both can be triggered by similar environmental stimuli, such as alcohol consumption, stress, and photic stimuli, probably due to both being forms of myoclonic epilepsy. Both disorders may be accompanied by psychological symptoms, such as depression, and they may worsen with age. Patients may present with normal MRIs, even with abnormal activity observed on EEGs. However, such similarities on the surface may lead to clinical misdiagnoses if an individual is not thoroughly and properly examined.

Despite such similarities, the two types differ in terms of genetic factors and inheritance patterns. While JME and FAME may be inherited through autosomal dominant means, this mostly only occurs with familial JME, as it does not have one definite inheritance pattern. Some cases of JME may be inherited through sporadic means without any familial ties, while others may be passed down from generation to generation. However, even as it's passed down consistently, the trait may not be expressed at all, only providing the affected individual with abnormal EEG activity and no real symptoms. While this

**Table 3** This table provides clinical background context for FAME, JME, and other myoclonic tremor disorders such as ET and PMEs-ULD, highlighting their respective ages of onset, syndromes, phenotypes, medication, and prognosis. Adapted from <sup>36</sup>.

| Characteristics          | FAME                                                                   | ET                                                                       | PMEs-ULD                                                                              | JME                                                                                                    |
|--------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Family History           | Familial clustering                                                    | Sporadic/50%-70% familial clustering <sup>66</sup>                       | Sporadic                                                                              | Sporadic/familial clustering                                                                           |
| Genetics basis           | Autosomal dominant                                                     | Heterogenous/autosomal dominant <sup>66</sup>                            | Autosomal recessive <sup>67</sup>                                                     | Heterogenous                                                                                           |
| Onset age                | After 24 years <sup>22</sup>                                           | Usually after 40 years <sup>66</sup>                                     | Usually 6–16 years, <sup>68</sup> with a peak at 12–13 years <sup>69</sup>            | Usually 12–18 years <sup>70,71</sup>                                                                   |
| Core phenotype           | Nonepileptic cortical myoclonus; epileptic seizures                    | Isolated bilateral action tremor                                         | Epileptic cortical myoclonus; GTCs; ataxia <sup>69</sup>                              | Epileptic cortical myoclonus; GTCs; absence seizures                                                   |
| Myoclonus/tremor feature | Myoclonus: mainly in distal muscles; 9–18 Hz <sup>72</sup>             | Tremor: bilateral, including head or voice tremor; 4–12 Hz <sup>72</sup> | Myoclonus: mainly in proximal muscles                                                 | Myoclonus: mainly in proximal muscles                                                                  |
| GTCs features            | Infrequent; mostly during wakefulness                                  | –                                                                        | Infrequent in the early stage, deteriorating with age; upon awakening or during sleep | Infrequent; mostly upon awakening                                                                      |
| <b>EMG features</b>      |                                                                        |                                                                          |                                                                                       |                                                                                                        |
| Burst patterns           | Arrhythmic                                                             | Rhythmic                                                                 | Arrhythmic                                                                            | Arrhythmic                                                                                             |
| g-SEP                    | +                                                                      | –                                                                        | +                                                                                     | +(35%-50% <sup>73</sup> )                                                                              |
| C-reflex                 | +                                                                      | –                                                                        | +                                                                                     | +                                                                                                      |
| <b>EEG features</b>      |                                                                        |                                                                          |                                                                                       |                                                                                                        |
| JLA                      | +                                                                      | –                                                                        | +                                                                                     | +                                                                                                      |
| PDR                      | Normal or mild slow                                                    | Normal                                                                   | Normal or mild slow                                                                   | Normal                                                                                                 |
| IEDs                     | GSWDs or focal SWs of occipital dominance; increase during wakefulness | –                                                                        | GSWDs or focal SWs of parietal and occipital dominance; increase during sleep         | 3–6 Hz GSWDs or PSWs of frontal predominance <sup>74</sup> ; increase at sleep onset or upon awakening |
| IPS                      | PPR up to 80% <sup>22</sup>                                            | –                                                                        | PPR up to 80%, alleviate after 10–15 years <sup>75</sup>                              | PPR up to 30% by regular IPS; 90% by enhanced and prolonged IPS <sup>83</sup>                          |
| Medication               | Responsive to ASMs; first-line: VPA/LEV with CLN                       | Responsive to $\beta$ -blockers; first-line PR                           | Drug-resistant; polytherapy needed                                                    | Responsive to ASMs; high relapse rate upon withdrawal <sup>76</sup>                                    |
| Cognitive function       | Normal or mild decline                                                 | Normal or mild medicine                                                  | Mild or moderate decline <sup>69</sup>                                                | Normal                                                                                                 |
| Structural MRI           | Normal or slight cerebellar atrophy                                    | Normal                                                                   | Nonspecific cortical and/or cerebellar atrophy <sup>77</sup>                          | Normal                                                                                                 |
| Pathology                | PC loss with morphological changes                                     | PC loss with morphological changes <sup>66</sup>                         | PC loss <sup>56</sup>                                                                 | Normal                                                                                                 |
| Prognosis                | Mildly progressive; remains good with appropriate treatment            | Remains good with appropriate treatment                                  | Rapidly progressive; from disability to lethal entity                                 | Remains good with appropriate treatment                                                                |

can happen with FAME, more often than not, the trait itself is inherited, and the symptoms show; it is clearly known to be an autosomal dominant disorder. In addition to their inheritance patterns, both epilepsies are caused by different reasons. JME is caused by the variants in genes such as GABRA1 and EFHC1. These mutations interfere with normal neuron signaling and development. On the other hand, FAME is caused by intronic repeat expansions within genes such as SAMD12 and STARD7, not impacting the function of the gene itself but rather its ability to regulate cellular processes and signaling properly. In addition, FAME's genes have confirmed chromosome linkages while JME does not. The suspected epigenetic factors involved in FAME, such as DNA methylation, are far more testable due to evidence found in other repeat expansion neurological disorders; such research has not been conducted on JME yet. Even so, JME's impact may be modulated by hormones and environmental triggers.

Such differences highlight the need for different technologies to be present in epilepsy screenings in order to gather correct data for future research and clinical prescriptions. While

new sequencing technology may be beneficial for JME, FAME requires technology that will be able to detect long repeat expansions, or rather long-read sequencing, which is not typically seen in epilepsy clinics.

One limitation in this review may include the lack of perspectives on the topics discussed, as many resources shared similar opinions, with some being based on each other. The different ranges of the sample sizes studied, the lack of research conducted on clinical trials for humans, animals, and cells alike, and uncertainty regarding how this paper's topic clearly ties into the ages of onset for JME and FAME possibly limited the scope this study provided. Several factors, such as heterogeneity, penetrance, polygenic risk, and environmental triggers were not explicitly connected or shown to influence the age of onset in JME or FAME too. Additionally, all resources used for this literature review were found on Google Scholar, meaning that some data from this academic paper selection may not be as diverse as if other databases were used or a meta-analysis was conducted.

As scientists continue to research JME and FAME, greater

focus should be placed on discovering epigenetic influences on JME penetrance and the inheritance patterns behind the disease. Additionally, further research should be conducted on developing more advanced methods for detecting repeat expansions in FAME, and the mechanisms connecting FAME's repeat expansions to heightened neuron activity. Understanding these points in these forms of epilepsy could potentially lead to more efficient and accurate diagnoses and treatments.

## References

- 1 Epilepsy Foundation, Types of Seizures. Epilepsy Foundation. Retrieved August 2, 2025., <https://www.epilepsy.com/what-is-epilepsy/seizure-types>.
- 2 R. Khan, Idiopathic Epilepsy: Overview, Causes and Treatments Options. Revive Research Institute. Retrieved August 2, 2025., <https://www.reviveresearch.org/blog/idiopathic-epilepsy/>.
- 3 U.S. National Library of Medicine, Juvenile myoclonic epilepsy. MedlinePlus. Retrieved August 2, 2025., <https://medlineplus.gov/genetics/condition/juvenile-myoclonic-epilepsy/>.
- 4 P. Striano and C. Nobile, The genetic basis of juvenile myoclonic epilepsy. *The Lancet Neurology*. Vol. 17, no. 6, pg. 493–495, 2018., [https://doi.org/10.1016/S1474-4422\(18\)30173-X](https://doi.org/10.1016/S1474-4422(18)30173-X).
- 5 C. S. Camfield, P. Striano, and P. R. Camfield, Epidemiology of juvenile myoclonic epilepsy. *Epilepsy and Behavior*. Vol. 28, S1, pg. S15–S17, 2013., <https://doi.org/10.1016/j.yebeh.2012.06.024>.
- 6 G. A. Uzun and B. Baykan, Familial Adult Myoclonic Epilepsy: Clinical and Genetic Approach to an Under-recognized Disease. *Noro psikiyatri arsivi*. Vol. 60, no. 2, pg. 174–177, 2023., <https://doi.org/10.29399/npa.28252>.
- 7 I. Lagorio, F. Zara, S. Striano, and P. Striano, Familial adult myoclonic epilepsy: A new expansion repeats disorder. *Seizure: European Journal of Epilepsy*. Vol. 67, pg. 73–77, 2019., <https://doi.org/10.1016/j.seizure.2019.03.009>.
- 8 B. G. Giraldez, J. M. Serratos, S. Striano, A. Ikeda, P. Striano, and A. Coppola, Familial adult myoclonus epilepsy: Clinical findings, disease course, and comorbidities. *Epilepsia*. Vol. 64, S9–S13, 2023., <https://doi.org/10.1111/epi.17595>.
- 9 M. Gilsoul, T. Grisar, A. V. Delgado-Escueta, L. de Nijs, and B. Lakaye, Subtle Brain Developmental Abnormalities in the Pathogenesis of Juvenile Myoclonic Epilepsy. *Frontiers in cellular neuroscience*. Vol. 13, 433, 2019., <https://doi.org/10.3389/fncel.2019.00433>.
- 10 T. V. Kodankandath, D. Theodore, and D. Samanta, Generalized Tonic-Clonic Seizure. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing, 2025. Updated July 3, 2023., <https://www.ncbi.nlm.nih.gov/sites/books/NBK554496/>.
- 11 O. S. Shilkina, S. N. Zbova, E. A. Domoratskaya, and D. V. Dmitrenko, Clinical and genetic characteristics of juvenile myoclonic epilepsy. *Personalized Psychiatry and Neurology*. Vol. 1, no. 2, pg. 95–105, 2021., <https://doi.org/10.52667/2712-9179-2021-1-2-95-105>.
- 12 M. A. Corbett, T. Kroes, L. Veneziano, M. F. Bennett, R. Florian, A. L. Schneider, A. Coppola, L. Licchetta, S. Franceschetti, A. Suppa, A. Wenger, D. Mei, M. Pendziwiat, S. Kaya, M. Delledonne, R. Straussberg, L. Xumerle, B. Regan, D. E. Crompton, and J. Gecz, Intronic ATTTC repeat expansions in STARD7 in familial adult myoclonic epilepsy linked to chromosome 2. *Nature Communications*. Vol. 10, Article 4920, 2019., <https://doi.org/10.1038/s41467-019-12671-y>.
- 13 A. Arslan, Pathogenic variants of human GABRA1 gene associated with epilepsy: A computational approach. *Heliyon*. Vol. 9, no. 9, e20218, 2023., <https://doi.org/10.1016/j.heliyon.2023.e20218>.
- 14 P. Cossette, L. Liu, K. Brisebois, H. Dong, A. Lortie, M. Vanasse, J. M. Saint-Hilaire, L. Carmant, A. Verner, W. Y. Lu, Y. T. Wang, and G. A. Rouleau, Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nature Genetics*. Vol. 31, no. 2, pg. 184–189, 2002., <https://doi.org/10.1038/ng885>.
- 15 S. Ma, M. A. Blair, B. Abou-Khalil, A. H. Lagrange, C. A. Gurnett, and P. Hadera, Mutations in the GABRA1 and EFHC1 genes are rare in familial juvenile myoclonic epilepsy. *Epilepsy research*. Vol. 71, no. 2–3, pg. 129–134, 2006., <https://doi.org/10.1016/j.eplepsyres.2006.06.001>.
- 16 U.S. National Library of Medicine, EFHC1 gene. MedlinePlus Genetics. Retrieved August 3, 2025., <https://medlineplus.gov/genetics/gene/efhc1/>.
- 17 P. K. Raju, P. Satishchandra, S. Nayak, V. Iyer, S. Sinha, and A. Anand, Microtubule-associated defects caused by EFHC1 mutations in juvenile myoclonic epilepsy. *Human mutation*. Vol. 38, no. 7, pg. 816–826, 2017., <https://doi.org/10.1002/humu.23221>.
- 18 C. L. Kniffin, Entry - 618073 - sterile alpha motif domain-containing protein 12; SAMD12 - OMIM - (omim.org). Online Mendelian Inheritance in Man, 2018., <https://omim.org/entry/618073>.
- 19 National Center for Biotechnology Information, Sterile alpha motif (SAM) domain. In Conserved Domain Database (CDD). Retrieved August 3, 2025., <https://www.ncbi.nlm.nih.gov/Structure/cdd/cddsrv.cgi?uid=cd0948>.
- 20 Weizmann Institute of Science, SAMD12 gene: Sterile alpha motif domain containing 12. GeneCards. Retrieved August 3, 2025., <https://www.genecards.org/cgi-bin/carddisp.pl?gene=SAMD12>.
- 21 H. Ishiura, K. Doi, J. Mitsui, et al., Expansions of intronic TTTCa and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nature Genetics*. Vol. 50, pg. 581–590, 2018., <https://www.nature.com/articles/s41588-018-0067-2>.
- 22 Z. Cen, Z. Jiang, Y. Chen, X. Zheng, F. Xie, X. Yang, X. Lu, Z. Ouyang, H. Wu, S. Chen, H. Yin, X. Qiu, S. Wang, M. Ding, Y. Tang, F. Yu, C. Li, T. Wang, H. Ishiura, S. Tsuji, and W. Luo, Intronic pentanucleotide TTTCa repeat insertion in the SAMD12 gene causes familial cortical myoclonic tremor with epilepsy type 1. *Brain: a journal of neurology*. Vol. 141, no. 8, pg. 2280–2288, 2018., <https://doi.org/10.1093/brain/awyl60>.
- 23 Y. Horibata and H. Sugimoto, StarD7 mediates the intracellular trafficking of phosphatidylcholine to mitochondria. *The Journal of biological chemistry*. Vol. 285, no. 10, pg. 7358–7365, 2010., <https://doi.org/10.1074/jbc.M109.056960>.
- 24 J. Flores-Martin, V. Rena, S. Angeletti, G. M. Panzetta-Dutari, and S. Genti-Raimondi, The Lipid Transfer Protein StarD7: Structure, Function, and Regulation. *International journal of molecular sciences*. Vol. 14, no. 3, pg. 6170–6186, 2013., <https://doi.org/10.3390/ijms14036170>.
- 25 R. T. Florian, F. Kraft, E. Leitão, S. Kaya, S. Klebe, E. Magnin, A. F. van Rootselaar, J. Buratti, T. Kühnel, C. Schröder, S. Giesselmann, N. Tschernoster, J. Altmueller, A. Lamiral, B. Keren, C. Nava, D. Bouteiller, S. Forlani, L. Jornea, R. Kubica, and C. Depienne, Unstable TTTTA/TTTCa expansions in MARCH6 are associated with Familial Adult Myoclonic Epilepsy type 3. *Nature communications*. Vol. 10, no. 1, 4919, 2019., <https://doi.org/10.1038/s41467-019-12763-9>.
- 26 P. Yeetong, M. Pongpanich, C. Srichomthong, A. Assawapitaksakul, V. Shotelersuk, N. Tantirukdham, C. Chunharas, K. Suphaeetiporn, and V. Shotelersuk, TTTCa repeat insertions in an intron of YEATS2 in benign adult familial myoclonic epilepsy type 4. *Brain: a journal of neurology*. Vol. 142, no. 11, pg. 3360–3366, 2019., <https://doi.org/10.1093/brain/awz267>.
- 27 L. Lo Piccolo, R. Yeewa, S. Pohsa, T. Yamsri, D. Calovi, J. Phetcharaburanin, M. Suksawat, T. Kulthawatsiri, V. Shotelersuk, and S. Jantrapirom, FAME4-associating YEATS2 knockdown impairs dopaminergic synaptic

- 
- integrity and leads to seizure-like behaviours in *Drosophila melanogaster*. *Progress in neurobiology*. Vol. 233, 102558, 2024., <https://doi.org/10.1016/j.pneurobio.2023.102558>.
- 28 A. V. Delgado-Escueta, B. P. Koeleman, J. N. Bailey, M. T. Medina, and R. M. Durón, The quest for juvenile myoclonic epilepsy genes. *Epilepsy & behavior: E&B*. Vol. 28, Suppl. 1, pg. S52–S57, 2013., <https://doi.org/10.1016/j.yebeh.2012.06.033>.
  - 29 A. M. Yacoub, A. A. Mahasneh, A. Yassin, R. F. Almomani, S. Aqaileh, and A. H. Al-Mistarehi, Whole exome sequencing revealed ultra-rare genetic variations in juvenile myoclonic epilepsy. *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. Vol. 46, no. 2, pg. 899–910, 2025., <https://doi.org/10.1007/s10072-024-07874-1>.
  - 30 National Cancer Institute, Definition of incomplete penetrance - NCI Dictionary of Cancer Terms - NCI. Retrieved August 2, 2025., <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/incomplete-penetrance>.
  - 31 S. Kumar, O. R. Shanker, J. Banerjee, M. Tripathi, P. S. Chandra, and A. B. Dixit, Epigenetics in epilepsy. *Progress in molecular biology and translational science*. Vol. 198, pg. 249–269, 2023., <https://doi.org/10.1016/bs.pmbts.2023.01.005>.
  - 32 F. He and P. K. Todd, Epigenetics in nucleotide repeat expansion disorders. *Seminars in neurology*. Vol. 31, no. 5, pg. 470–483, 2011., <https://doi.org/10.1055/s-0031-1299786>.
  - 33 T. D. Bird, Myotonic dystrophy type 1. In *GeneReviews*. University of Washington, Seattle. Retrieved August 3, 2025., <https://www.ncbi.nlm.nih.gov/books/NBK1165/>.
  - 34 A. D. Otten and S. J. Tapscott, Triplet repeat expansion in myotonic dystrophy alters the adjacent chromatin structure. *Proceedings of the National Academy of Sciences of the United States of America*. Vol. 92, no. 12, pg. 5465–5469, 1995., <https://doi.org/10.1073/pnas.92.12.5465>.
  - 35 I. E. Scheffer, The Key to FAME: Intronic Repeat Expansions Cause Human Epilepsies. *Epilepsy currents*. Vol. 18, no. 4, pg. 238–239, 2018., <https://doi.org/10.5698/1535-7597.18.4.238>.
  - 36 Y. Lu, Y. Ge, R. Wang, Y. Zheng, J. Zhou, Z. Wang, C. Shen, S. Wang, L. Hu, B. Wang, Z. Cen, W. Luo, M. Ding, S. Wang, and Y. Ding, Familial adult myoclonus epilepsy: A comprehensive diagnostic strategy for clinical practice. *Epilepsia*. Vol. 66, pg. 4107–4121, 2025., <https://doi.org/10.1111/epi.18568>.